REMARKS

Claim 82 is pending in the application, and was finally rejected in the Office Action dated August 11, 2005. In the present amendment, claim 82 is amended to clarify the nature of the claimed topical pharmaceutical composition. No new matter has been introduced by this amendment. Support is found throughout the specification, for example, at page 62, lines 15 and 24-25, and page 63, lines 22-25. Entry of this amendment is respectfully requested.

I. Interview Summary

Applicants thank the Examiner for the courtesy of a telephone interview on November 21, 2005. Examiner Cook and the undersigned discussed claim 82 in view of the references cited in the Final Office Action of August 11, 2005. The arguments of record were reiterated. The Examiner suggested that Applicants either amend claim 82 to further distinguish the prior art and reflect the unexpected results provided by the claimed composition formulated for topical administration, or revise claim 82 into a method of use claim, *e.g.*, a method of decreasing melanin production by applying the claimed compounds. The Examiner indicated that such a method of use claim reciting the same scope of compounds as claim 82 should be allowable. Applicants also thank the Examiner's Supervisor, Examiner Low, for addressing these same points in telephone conversations with the with the undersigned and Dr. Ann-Louise Kerner due to Examiner Cook's absence from the office.

II. Rejection of claim 82 under 35 U.S.C. § 103(a)

In the Final Office Action mailed on August 11, 2005, claim 82 was again rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 3,389,051 to Kagan ("Kagan") in view of CA117:239545. Applicants respectfully traverse this rejection.

Applicants' amended claim 82 recites the following:

> A pharmaceutical composition for reducing skin pigmentation, comprising a skin pigmentation reducing effective amount of a compound that effects an alteration in late endosomal/lysosomal trafficking in a skin cell and a *dermatologically* acceptable carrier, wherein the pharmaceutical composition is an *ointment, cream, lotion or emulsion* formulated for *percutaneous absorption* by

> *topical* administration, and wherein the compound that *effects the alteration in late endosomal/lysosomal trafficking* is selected from the group consisting of: [chemical structures II-VIII]. (emphasis added).

Kagan discloses methods for reducing cholesterol in the body by administering particular chemical compounds (col. 1, lines 1-20). The disclosure of Kagan is focused on compositions for oral administration or injection for reducing cholesterol levels, and does not teach or suggest *topical* administration of the disclosed cholesterol lowering compositions formulated for *any* purpose, let alone for percutaneous absorption (*see, e.g.,* col. 4, lines 69-75; col. 5, lines 61-66; Examples 1-8; claims 1-2).

CA117:239545 discloses a controlled release self-adhesive transdermal and topical delivery system based on biocompatible polyurethane elastomers. CA117:239545 does not disclose or suggest administration of any of the compounds recited in claim 82, and does not teach or suggest using anything for effecting an alteration in late endosomal/lysosomal trafficking.

A. Claim 82 is not *prima facie* obvious over the cited references.

To support a *prima facie* case of obviousness, the cited references must teach or suggest every element of the claimed invention, and there must be some suggestion or motivation to combine the teachings of the cited references. The motivation to combine must be found in the prior art, and must not be based on impermissible hindsight in view of Applicants' disclosure. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1369-1370 (Fed. Cir. 2000). Furthermore, the showing of motivation to combine must be clear and particular, based on actual evidence, and not merely broad conclusory statements regarding the teachings of multiple references. *Id.* at 1370-1371 ("[A] rejection cannot be predicated on the mere identification in [the prior art] of individual components of claimed limitations. Rather, *particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.*" (emphasis added)).

Claim 82 is not *prima facie* obvious over Kagan and CA117:239545, alone or in combination. Neither of the cited references provides any teaching regarding a *topical pharmaceutical composition* for *reducing skin pigmentation* with a compound that *effects an*

alteration in late endosomal/lysosomal trafficking in a skin cell as claimed. In the present amendment, claim 82 has been amended to further emphasize that the claimed pharmaceutical composition is specifically formulated for topical administration to reduce skin pigmentation. Amended claim 82 specifies that the composition includes a *dermatologically* acceptable carrier, and takes the form of an *ointment, cream, lotion or emulsion* formulated for *percutaneous absorption* by topical administration.

The Office Action of September 11, 2003 states that Kagan discloses a compound corresponding to compound VIII of Applicants' claim 82, and that it would have been obvious to deliver this compound in a topical delivery system as disclosed by CA117:239545. The Final Office Action of April 8, 2005 states further that Kagan's failure to disclose a topical or transdermal delivery system does not mean the reference intended to exclude such delivery systems, because the reference does not state that the disclosed compounds cannot be used in such forms.

Applicants respectfully submit that the Examiner still has not satisfied the burden of identifying and providing particular evidence demonstrating an affirmative motivation to combine the teachings of Kagan, relating to oral or parenteral cholesterol lowering compositions, with the teachings of CA117:239545 directed to a transdermal and topical delivery system, *other than impermissible hindsight based on Applicants' disclosure.* Kagan's failure to explicitly prohibit topical application of the disclosed compounds does not provide the requisite motivation to combine. Indeed, Kagan effectively teaches away from the use of transdermal or topical delivery systems such as the one disclosed by CA117:239545.

More specifically, Kagan discloses a wide range of *oral* and *parenteral* formulations for administering the disclosed cholesterol lowering compounds (*see, e.g.,* col. 4, line 69 - col. 5, line 66; Examples 1-8). For example, at column 4, lines 70-75, Kagan states that "the novel compositions are suitably presented for administration in unit dosage form as tablets, pills, capsules, powders, wafers, cachets, granules, sterile parenteral solutions or suspensions in aqueous or oil vehicles, oral aqueous or oil dispersions, including syrups and elixirs, and the like." However, Kagan does *not* disclose specific compositions formulated for percutaneous absorption by *topical* administration, although the general concept of topical pharmaceutical compositions has been well known for many years. The Final Office Action of August 11, 2005 states that Kagan discloses solutions, which can be applied topically. However, the passage cited

as allegedly supporting this statement, col. 4, lines 73-75 of Kagan, refers only to *parenteral* solutions, as noted above. Thus, this passage suggests administration of solutions via *injection*, *not* topical administration. Indeed, by disclosing numerous oral and parenteral dosage forms but failing to disclose topical formulations, the teachings of Kagan suggest to one of ordinary skill in the art that the disclosed compositions would not be effective for their intended purpose when administered topically. Accordingly, the only possible motivation to combine the compounds disclosed by Kagan with the topical and transdermal delivery system disclosed in CA117:239545 would be based on *improper hindsight in view of Applicants' disclosure.*

The Office Action of August 11, 2005 cites *In re McLaughlin*, 170 U.S.P.Q. 209, for the following proposition:

> Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and *does not include knowledge gleaned only from the applicant's disclosure*, such a reconstruction is proper. (Emphasis added).

Applicants respectfully submit that, as detailed above, in this case the alleged motivation to combine *requires reliance on Applicants' disclosure* and, accordingly, is *improper. See, e.g., In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("[T]he Patent and Trademark Office found prior art statements that in the abstract appeared to suggest the claimed limitation. But, there was no finding as to the *specific understanding or principle within the knowledge of a skilled artisan* that would have motivated one *with no knowledge of Kotzab's invention* to make the combination in the manner claimed." (emphasis added)).

B. The claimed compositions provide unexpected results that overcome any alleged *prima facie* case of obviousness.

Furthermore, even if a *prima facie* case of obviousness had been established, it would be rebutted by the unexpected effects of the claimed compositions in reducing skin pigmentation, as described in the specification (*see, e.g.*, page 7, lines 8-15; page 8, line 32 – page 11, line 3; page 16, lines 21-31; page 18, lines 13-16; page 19, lines 1-6; page 50, lines 23-29; page 56, lines 6-12; Example 6; and Figures 15-16). *See, e.g., In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). The inventors determined that agents capable of modifying late endosomal/lysosomal trafficking

(such as the compounds recited in claim 82) are useful for reducing skin pigmentation, because they alter the trafficking of proteins necessary for melanin synthesis, and decrease melanin production. Prior to this discovery, one of ordinary skill in the art would not have expected the compounds recited in claim 82 to have an effect on melanin production, and thus would not have been motivated to apply the compounds in topical formulations for percutaneous absorption for reducing skin pigmentation as claimed. The experimental results described in Example 6 and illustrated in Figures 15-16 demonstrate the previously unknown and unexpected effect on skin pigmentation of the compounds recited in claim 82. These results demonstrate for the first time that compounds II-VIII significantly decrease melanin production in melanocytes (*see* Specification, page 79, lines 18-27; page 50, lines 23-29; and Figures 15-16). Thus, as described and demonstrated by experimental evidence presented in the specification, the claimed topical compositions provide the previously unknown and beneficial effect of decreasing melanin production, and thus reducing skin pigmentation.

The language of Applicants' amended claim 82 specifically reflects these unexpected results, emphasizing that the claimed "pharmaceutical composition *for reducing skin pigmentation*" includes a "*skin pigmentation reducing effective amount* of a compound that *effects an alteration in late endosomal/lysosomal trafficking in a skin cell.*" Furthermore, the claimed pharmaceutical composition includes a "*dermatologically* acceptable carrier," and takes the form of "*an ointment, cream, lotion or emulsion* formulated for *percutaneous absorption* by *topical administration.*" Thus, the claim explicitly refers to and incorporates the unexpected results demonstrating the non-obviousness of the claimed compositions, namely, the unexpected effects of the agents capable of modifying late endosomal/lysosomal trafficking in reducing skin pigmentation when applied in a composition formulated for topical administration.

The Final Office Action of August 11, 2005 states that the unexpected results of the claimed composition in reducing skin pigmentation are not persuasive in overcoming the alleged *prima facie* case of obviousness, because the claim does not recite a method of use. Applicants respectfully disagree. Nonobviousness of a claimed chemical composition can be established based on the composition's unexpected activity in performing a certain function. *See, e.g., In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) (unexpected results demonstrating herbicidal activity in two crops established nonobviousness of claimed chemical compound and corresponding herbicidal composition); *see also, In re Soni*, 54 F.3d 746 (Fed. Cir. 1995) (PTO erred in giving

insufficient weight to unexpected results in specification regarding performance properties of claimed polymer composition). In this case, the unexpected effects of the claimed topical compositions in reducing skin pigmentation, as described in the specification, are sufficient to overcome any alleged *prima facie* case of obviousness.

In sum, *prima facie* obviousness has not been established, and even if there were a *prima facie* case, it would be rebutted by the unexpected effects of the claimed compositions in reducing skin pigmentation. Accordingly, claim 82 is not obvious in view of the cited references alone or in combination, and Applicants respectfully request that the present rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

III. Conclusion

In view of the amendment and arguments set forth above, Applicants respectfully submit that the rejections contained in the Final Office Action mailed on August 11, 2005 have been overcome, and that the pending claim is in condition for allowance.

Applicants hereby petition for a two-month extension of time to respond to the Final Office Action of August 11, 2005. Please deduct the $450.00 fee for this purpose from our Deposit Account No. 08-0219. Please also charge the $790.00 fee for this Request for Continued Examination to our Deposit Account No. 08-0219. No other fees are believed to be due in connection with this correspondence. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

Dated: 1/11/06

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